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Patients in Whom to Consider Genetic Evaluation and Testing for Hereditary Colorectal Cancer Syndromes

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INTRODUCTION

Hereditary colorectal cancer syndromes (HCCS) confer markedly increased risks of colorectal and extracolonic tumors (Table 1). Many individuals with HCCS go unrecognized until the time of a cancer diagnosis, whereas others are identified through genetic testing based on family history of cancer. Frequently, gastroenterologists are a first touch point for patients with HCCS and must be prepared to recognize “the needles in the haystack” and identify who should undergo genetic risk assessment and appropriate evaluation and testing.

Individuals in whom to consider evaluation for HCCS

Evaluation and testing for HCCS should be considered in individuals with suggestive personal and family characteristics (Table 2).

Colorectal cancer in patients younger than 50 years

Benign and malignant tumors occurring at an age less than 50 years increases the chances of HCCS. Studies of patients with early-onset colorectal cancer (CRC) found that 16%–18% carried germline genetic mutations (1,2). However, a cancer diagnosis in patients older than 50 years does not rule out the possibility of HCCS. In a study of unselected patients with CRC, 10% carried genetic mutations in CRC-associated genes (3).

Suspicious family cancer history

Family history of cancer is a hallmark of a heritable syndrome especially when family members develop the same or related cancers (i.e., CRC and endometrial cancer in the case of Lynch syndrome (LS) or colonic polyposis and thyroid cancer in the case of familial adenomatous polyposis [FAP]). Clinical tools based on personal and family cancer history can identify individuals to consider for LS testing (Table 3). Amsterdam II and revised Bethesda guidelines can be used to identify patients with LS but do not have ideal test characteristics with limitations in sensitivity and specificity, respectively. PREMM₅ has

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improved characteristics (4) and was implemented successfully in a community gastroenterology practice (5). A simple 3-question survey tool also can identify high-risk individuals with good sensitivity (6), and implementation of a modified version was feasible in an academic endoscopy center (7).

Tumor features of deficient mismatch repair

Testing all colon cancers (called universal testing) is a strategy to identify patients with LS. Interrogation of tumors for evidence of deficient mismatch repair (the hallmark of LS) is endorsed by numerous organizations including the US Multisociety Task Force (8) and the American College of Gastroenterology (9). Tumor testing involves staining biopsy or resection specimens for mismatch repair protein expression (called immunohistochemistry). The absence of expression of MLH1 and/or PMS2 or MSH2 and/or MSH6 is suggestive of LS with some caveats. An alternate approach is to perform microsatellite instability by polymerase chain reaction. Abnormal tumor testing requires patients to follow up with a risk assessment and genetic testing if appropriate. Although universal testing is becoming more widespread, follow-up of abnormal results remains variable and differs by medical center and race among other factors (10). When optimally implemented, universal testing has been found to be cost effective for LS and helps identify additional at-risk family members who benefit from surveillance (11).

>10–20 cumulative colonic adenomas

The most common adenomatous polyposis syndromes are FAP and MutYH-associated polyposis (MAP). FAP can be profuse (100s to 1000s of adenomas) or attenuated (10s to a 100 adenomas). Most patients with FAP have a family history of polyposis, although 25% can arise as a new mutation and would not report a family history of FAP. MAP, a recessive condition, is overwhelmingly an attenuated polyposis syndrome similar to attenuated FAP. Current guidelines recommend genetic testing for individuals with greater than 10–20 cumulative adenomas (9,12). Recently, mutations in polymerase proofreading genes, *POLE* and *POLD1*, and 2 copies of *NTHL1* and *MSH3* mutations have been associated with hereditary adenomatous polyposis as well as other cancers. In individuals of Ashkenazi Jewish ancestry, hereditary mixed polyposis syndrome associated with adenomas and polyps containing a mixture of hyperplastic and inflammatory changes has been associated with mutations in *GREM1* (13).

Numerous gastrointestinal hamartomatous polyps

Hamartomatous syndromes are recognized by the presence of hamartomas and cancer within and outside of the gastrointestinal tract. Juvenile polyposis syndrome and Peutz-Jeghers syndrome should be considered in individuals with greater than 3 colonic and greater than 2 small bowel hamartomas, respectively, as well as other clinical criteria. Cowden syndrome is associated with a high risk of nongastrointestinal and slightly increased risk of CRC and can manifest with a polyposis phenotype including several colonic polyp types such as hamartomas, ganglioneuromas, serrated polyp, and adenomas (14). A risk calculator can be used to assess probability of a PTEN mutation and guide genetic testing (<http://www.lerner.ccf.org/gmi/ccscore/>).

Numerous and large colonic serrated polyps

Serrated polyposis syndrome is defined clinically by revised 2019 World Health Organization criteria (Table 4). To date, a definitive genetic basis for this condition has not been established, and genetic testing is typically not offered.

HOW AND WHEN TO TEST FOR HCCS

Genetic counseling

Patients with suspected HCCS should meet with a genetic counselor or a provider knowledgeable in principles of genetic testing for pre-test and post-test counseling. During a precounseling session, personal and family histories as well as testing options and potential outcomes are reviewed if appropriate. If testing is pursued, post-test counseling involves reviewing results and implications. Additional issues such as insurance coverage, genetic discrimination, testing in family members, and family planning are discussed.

Multigene panel testing

Technological advances have revolutionized genetic testing enabling sequencing of many genes at the same time. Multigene panel tests enable assessment for multiple syndromes simultaneously and lower cost and reduced test “fatigue” for patients. In the case of genetic evaluation for multiple adenomas, multigene panel testing shows increasing yield with increasing number of polyps, although yield decreases with older patient age. For patients with 10–19 cumulative adenomas, germline mutations (primarily *APC* and *MutYH*) were detected in 4–8% of patients, while this rate was 7%–14% for 20–99 adenomas and 50% or greater for >100 adenomas (15,16). Depending on the panel used, genetic testing can have additional outcomes including the possibility of finding a mutation in less understood genes. Although risks and management are known for LS and polyposis syndromes, this is not the case for genes with low or moderate CRC risk (e.g., *CHEK2*, *ATM*, *TP53*, and 1 allele of *MutYH*) or genes with limited data on CRC risk (e.g., *AXIN2*, *NTHL1*, *MSH3*, *RNF43*, *GALNT12*, and *RPS20*) (12). Another outcome is finding an “unanticipated” mutation in a gene(s) that appear unrelated to personal or family history but for which management guidelines exist (e.g., *LS genes*, *BRCA1*, *BRCA2*, *CDH1*, *CDKN2A*, and *PALB2*). Finally, multigene panel testing increases the chance of identifying a variant of uncertain significance (VUS). A VUS should not be confused with a pathogenic variant because the health consequence of a VUS is not yet established and should not guide clinical management.

Timing of genetic testing

For syndromes with childhood onset (e.g., FAP, juvenile polyposis, and Peutz-Jeghers syndrome), genetic testing is performed in children. For families with LS, testing in family members should occur between ages 18–20 years since colonoscopy screening commences between ages 20 and 25 years. In newly diagnosed CRC with features of HCCS, genetic evaluation and testing before surgery allows shared decision-making about surgical options.

CONCLUSIONS

Gastroenterologists are in a unique position to recognize, diagnose, and manage HCCS. However, this requires providers to be equipped with knowledge and tools to identify at-risk individuals. In a busy clinical and endoscopic practice, time can be limited for extensive discussions about personal and family history. Implementation of short surveys, robust universal tumor testing protocols, educational efforts, and a team approach can help to overcome many barriers. There remain areas of uncertainty such as which genes should be included on panel tests, cancer risk estimates for less penetrant genes, interpretation of variants of uncertain significance, as well as lack of access and genetic counseling resources.

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Table 1.

Hereditary colorectal cancer syndromes

Syndrome		Gene(s)	Key features
Polypoid	Adenomatous polyps	FAP	<i>APC</i>
			10s-1000s of colonic adenomas; duodenal adenomas; fundic gland polyps; colon, duodenal, and thyroid cancer; desmoid tumors
	MAP		<i>MutYH</i>
Hamartomatous polyps			10s-100s colonic adenomas; duodenal adenomas; serrated polyps, lymphoid follicles, fundic gland polyps; colon, duodenal, and thyroid cancer
	Polymerase-proofreading polyposis		<i>POLE</i> and <i>POLD1</i>
	Juvenile polyposis		10s-100s colonic adenomas; endometrial cancer
			Hamartomas predominantly in the stomach and colon; gastric and colon cancer, hereditary hemorrhagic telangiectasia (<i>SMAD4</i> carriers)
	Peutz-Jeghers		<i>STK11</i>
Serrated polyps			Hamartomas predominantly in small bowel; pancreatic, breast, ovarian, and testicular, and lung cancer, lip, and buccal freckles
	PTEN-associated (e.g., Cowden)		<i>PTEN</i>
	Serrated polyposis syndrome		Multiple and large serrated polyps ^b
Inflammatory, hyperplastic, and adenomatous polyps			Ashkenazi Jewish ancestry; polyps of mixed histologies (serrated, inflammatory, and adenomas)
	Hereditary mixed polyposis syndrome		<i>GREM1</i>
			Polyps (hamartomas, adenomas, ganglioneuromas and others) in GI tract; large head circumference; esophageal glycogenic acanthosis; breast, thyroid, endometrial, renal, and colon cancer
CRC			Risk of endometrial, small bowel, stomach, pancreaticobiliary, urothelial, ovarian, sebaceous skin, and brain cancers
	Lynch syndrome		<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , and <i>EPCAM</i>
	Familial CRC type X		Individuals who meet Amsterdam I criteria but do not have genetic features of Lynch syndrome
	Other genes ^c		Features depending on mutated gene
			<i>CHEK2</i> , <i>ATM</i> , <i>TP53</i> , 1 allele of <i>MutYH</i>

CRC, colorectal cancer; FAP, familial adenomatous polyposis; MAP, MutYH-associated polyposis.

^a *RNF43* has been implicated in a small number of cases of serrated polyposis syndrome.

^b WHO criteria for serrated polyposis syndrome listed in Table 4.

^c Genes with limited data on CRC risk (*AXIN2*, *NTHL1*, *MSH3*, *GALNT12*, and *RPS20*) and genes that predispose to other cancer syndromes, but limited data on CRC risk (*BRCA1*, *BRCA2*, *CDH1*, *CDKN2A*, and *PALB2*) are often included on multigene panel tests; for some of these genes, data on appropriate clinical management are lacking and largely based on expert opinion.

Table 2.

Features that warrant evaluation and possible testing for HCCS

CRC in patients younger than 50 yr
Personal history of multiple cancers (e.g., CRC and endometrial cancer, colonic polyposis, and thyroid cancer)
Personal and family history suspicious for LS ^a
Tumor testing with deficient mismatch repair ^b
More than 10–20 cumulative colonic adenomas
More than 3 colonic hamartomas or 2 small bowel hamartomas ^c
Family members with known genetic diagnosis of HCCS

CRC, colorectal cancer; HCCS, hereditary colorectal cancer syndromes; LS, Lynch syndrome.

^aAssessed using tools such as Amsterdam II, revised Bethesda criteria, PREMM5 or a 3-question survey, see Table 3.

^bCaveats are when loss of MLH1/PMS2 or microsatellite instability is due to somatic methylation or double somatic mutations rather than germline mutation.

^cIn addition to other clinical criteria for juvenile polyposis syndrome, Peutz-Jeghers syndrome and Cowden syndrome.

Table 3.

Clinical tools for identification of LS

Tool	Criteria
Amsterdam II	<p>At least 3 relatives must have a cancer associated with LS (CRC, cancer of the endometrium, small bowel, ureter, or renal-pelvis); all of the following criteria should be present:</p> <ul style="list-style-type: none"> • One must be a first-degree relative of the other two; • At least 2 successive generations must be affected; • At least 1 relative with LS-associated cancer diagnosed under age 50yr; • FAP should be excluded
Revised Bethesda	<p>CRC from individuals should be tested for MSI in the following situations:</p> <ul style="list-style-type: none"> • CRC diagnosed in a patient who is younger than 50yr • Presence of synchronous, or metachronous, colorectal, or other LS-related tumors, regardless of age • CRC with MSI-high histology diagnosed in a patient who is younger than 60 yr • CRC diagnosed in a patient with 1 or more first-degree relatives with LS-related cancer, with one of the cancers being diagnosed under age 50 yr • CRC diagnosed in a patient with 2 or more first- or second-degree relatives with LS-related cancer regardless of age
PREMM ₅	http://premm.dfci.harvard.edu
3-Question survey	<p>(i) Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50 yr?</p> <ul style="list-style-type: none"> • Colon or rectal cancer • Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, and bladder), bile ducts, pancreas, or brain <p>(ii) Have you had any of the following conditions diagnosed before age 50 yr?</p> <ul style="list-style-type: none"> • Colon or rectal cancer • Colon or rectal polyps <p>(iii) Do you have 3 or more relatives with a history of colon or rectal cancer?</p> <ul style="list-style-type: none"> • Includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins

Adapted with permission from Syngal S, et al. (9).

CRC, colorectal cancer; FAP, familial adenomatous polyposis; LS, Lynch syndrome; MSI, microsatellite instability.

Table 4.

World Health Organization criteria for serrated polyposis syndrome (updated in 2019)

At least 5 serrated polyps proximal to the rectum all ≥ 5 mm, with at least 2 ≥ 10 mm
More than 20 serrated polyps of any size but distributed throughout the large bowel, with at least 5 proximal to the rectum

Polyp count is cumulative, and any histological subtype of serrated polyp is included in the final polyp count.

Adapted with permission from: Digestive System Tumours, 5th Edition, WHO Classification of Tumours Editorial Board, Serrated Polyposis, pp. 532–5, 2019.

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